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National Institute of Mental Health

New Frontiers: From Biological Psychiatry to Clinical Neuroscience

Thomas R. Insel, MD

Director, NIMH

Acting Director, NCATS

Disclosures: None

Federal employee: Public filing of all financial interests

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

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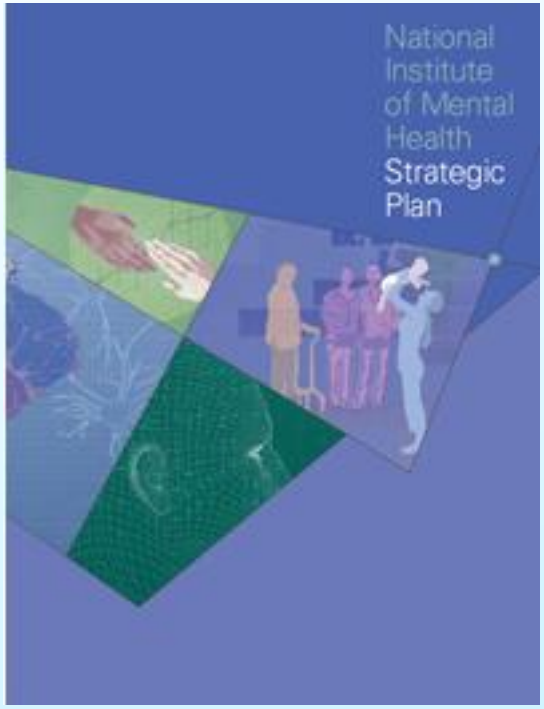
NIMH Strategic Plan

The 4 P's:

- Pathophysiology
- Preemptive
- Person-centered
- Public health impact



Multi-level Scientific Approach: Our Toolbox for Pathophysiology

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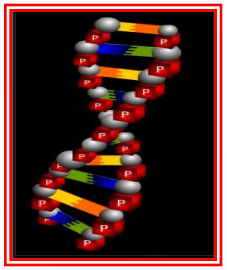



Molecules	Cells	Systems	Individual	Social
GWAS	Stem Cells	Electrode	Sensors	Web 2.0
Sequencing	RNAseq	Arrays	Eye gaze	Knowledge
Transgenics	Proteomics	Zebrafish	Cognitive	Management
Knock-outs	Optical	Imaging	Tools	Crowd Sourcing
Epigenetics	imaging	ChR-2	Epidemiology	
Databases	Databases	Databases	Databases	Databases

Genetics: Transforming Technologies
Sequencing Costs Drop Faster than Moore's Law

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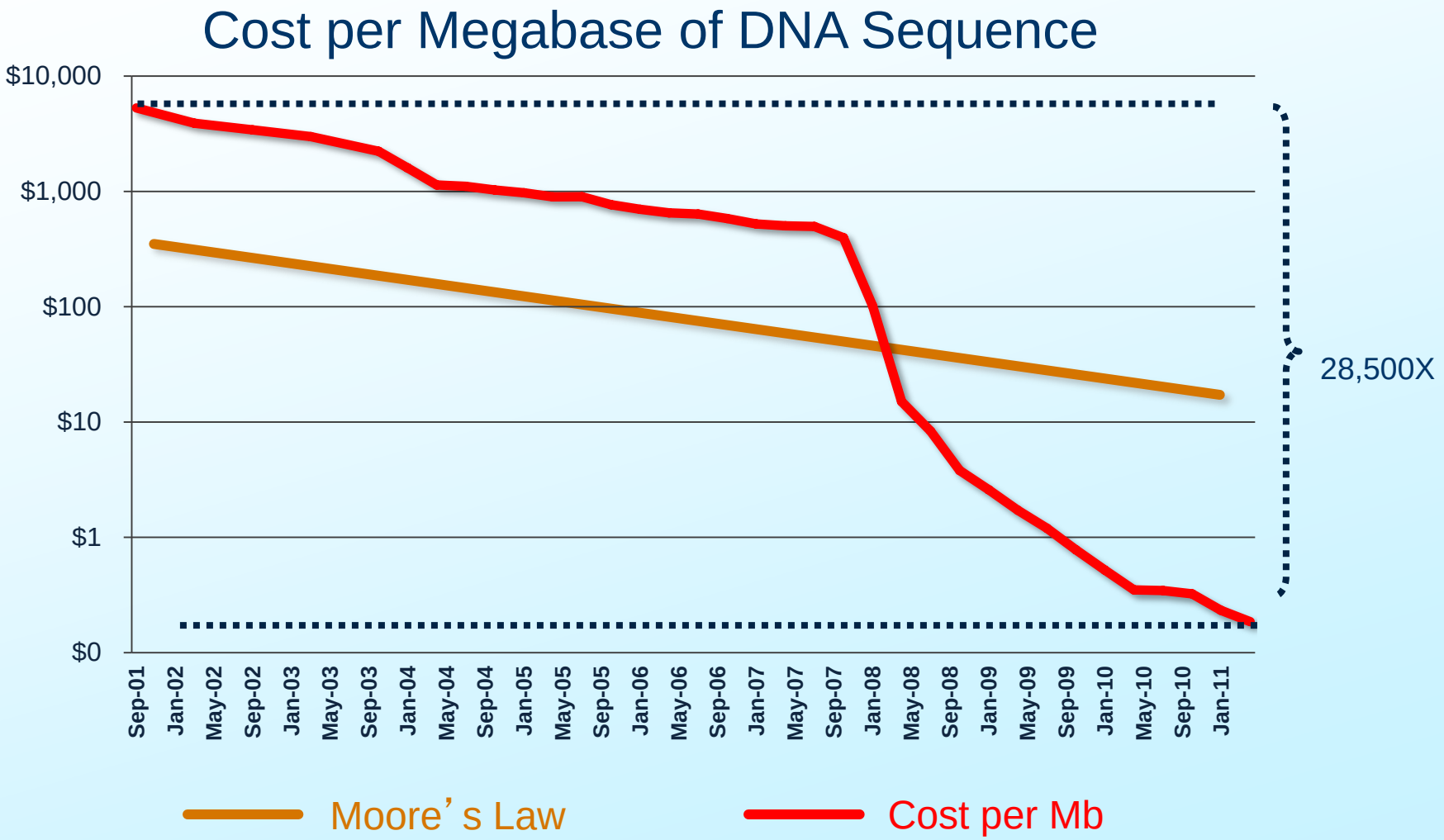

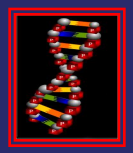

Genetics – What Have We Learned?

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- Genetic ≠ Inherited (spontaneous mutations are common)
- Genetic ≠ Causal (genes confer risk and resilience)
- Genetics may reveal pathways involved in risk and resilience
- Genetics provides a mechanism for experience to influence brain and behavior (epigenomics!)
- Genetics (genomics) is our most powerful tool for understanding individual variation (and that variation is huge!)

Genetics – What Have We Missed?

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Somatic Mutations

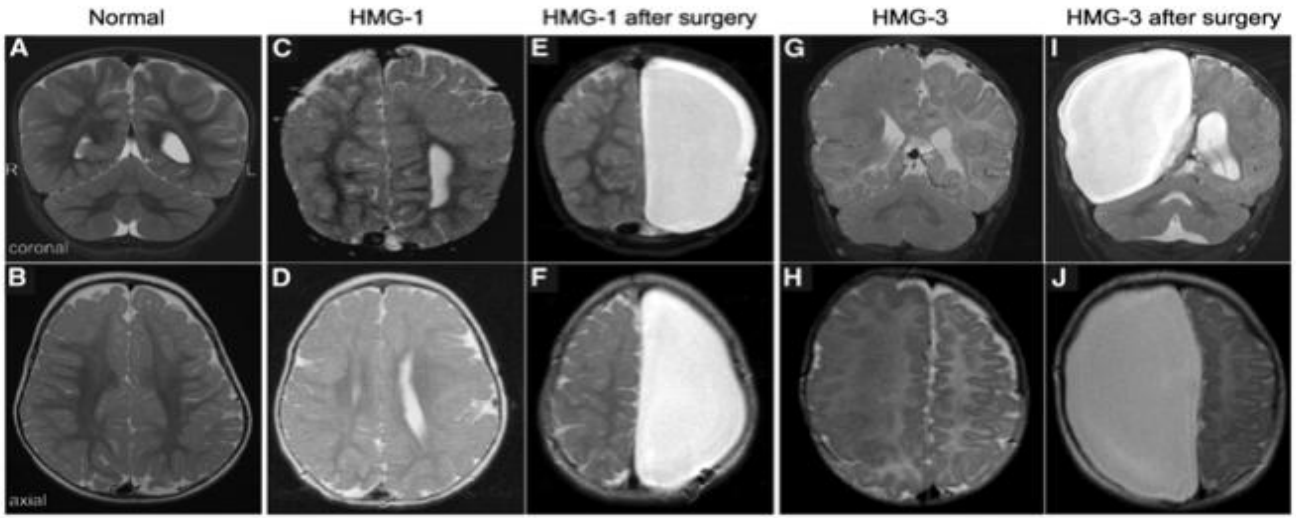
Cell, April 2012

Neuron
Report

Cell PRESS

Somatic Activation of *AKT3* Causes Hemispheric Developmental Brain Malformations

Annapurna Poduri,[1,4] Gilad D. Evrony,[2,5] Xuyu Cai,[2,5] Princess Christina Elhosary,[1] Rameen Beroukhim,[6,9,10,12,15] Maria K. Lehtinen,[2,3,7] L. Benjamin Hills,[2] Erin L. Heinzen,[16] Anthony Hill,[2] R. Sean Hill,[2,15] Brenda J. Barry,[2] Blaise F.D. Bourgeois,[1,4] James J. Riviello,[1,4,19] A. James Barkovich,[17] Peter M. Black,[13,18] Keith L. Ligon,[3,7,10,11,14] and Christopher A. Walsh[2,4,8,15,*]



Protective LOF Mutations as Drug Targets

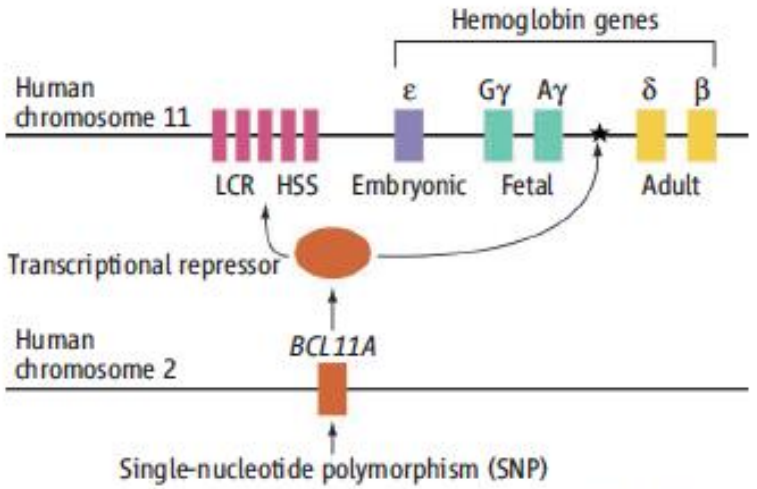
Human Fetal Hemoglobin Expression Is Regulated by the Developmental Stage-Specific Repressor *BCL11A*

Vijay G. Sankaran,[1,2] Tobias F. Menne,[1] Jian Xu,[1] Thomas E. Akie,[1] Guillaume Lettre,[3,4] Ben Van Handel,[5] Hanna K. A. Mikkola,[5] Joel N. Hirschhorn,[3,4] Alan B. Cantor,[1] Stuart H. Orkin[1,2,6,*]

Science
AAAS

- Mutant adult Hgb cannot bind O2
- Fetal Hgb spared
- Fetal Hgb reduced postnatally

Will blockade of a repressor of fetal Hgb lead to an effective treatment for Sickle Cell Anemia?



Expression		*BCL11A* SNP
Fetal hemoglobin	*BCL11A*	
Low	High	GG (homozygous)
High	Low	AA (homozygous)

Epigenetics – A Possible Target?

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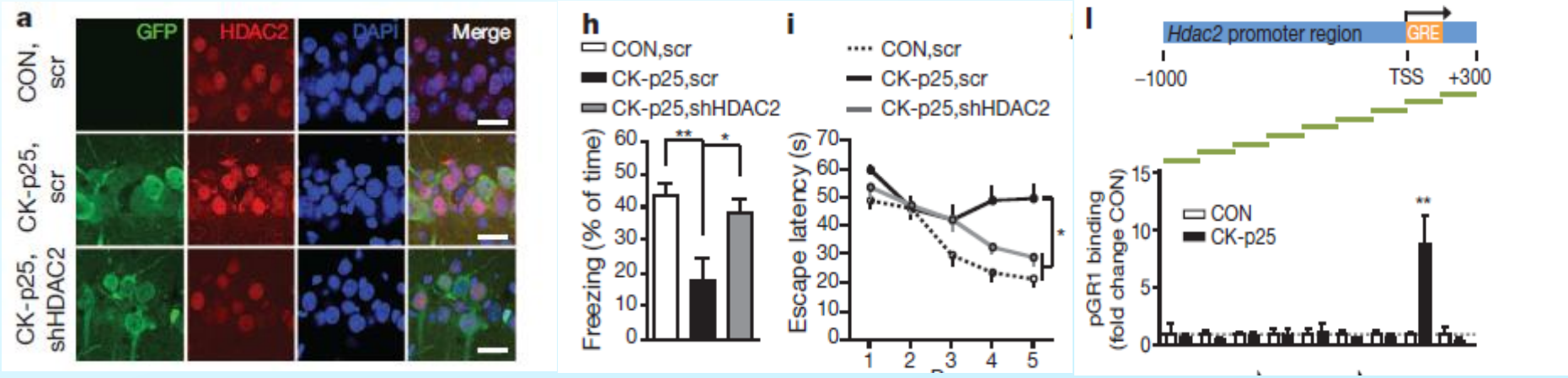
LETTER

March 2012

doi:10.1038/nature10849

An epigenetic blockade of cognitive functions in the neurodegenerating brain

Johannes Gräff[1,2,3], Damien Rei[1,2], Ji-Song Guan[1,2,3], Wen-Yuan Wang[1,2,3], Jinsoo Seo[1,2], Krista M. Hennig[3,4], Thomas J. F. Nieland[3], Daniel M. Fass[3,4], Patricia F. Kao[5], Martin Kahn[1], Susan C. Su[1,2], Alireza Samiei[1], Nadine Joseph[1,2,3], Stephen J. Haggarty[3,4], Ivana Delalle[5] & Li-Huei Tsai[1,2,3]



Transformative Technologies: Imaging Cells

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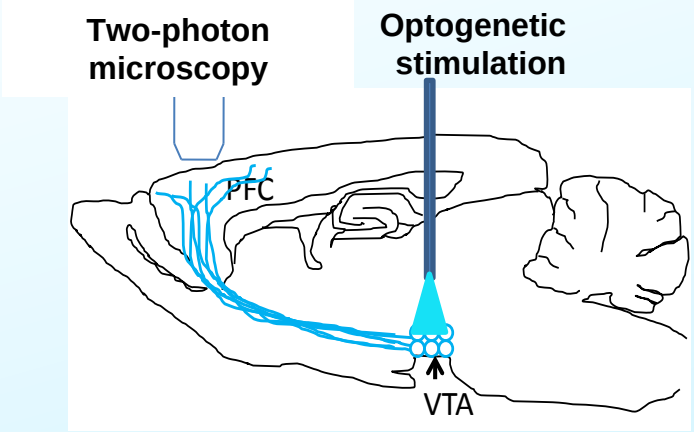
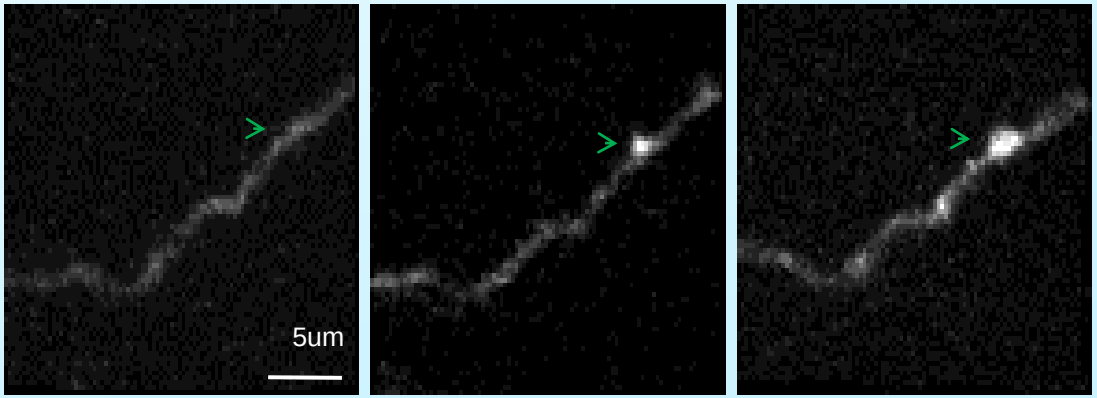
In Vivo Imaging of the Plasticity of Axonal Boutons on Mesoprefrontal Dopaminergic Innervations





Mastwal & Wang

before +2hr +24hr

Transformative Technologies – iPS cells

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Science

AAAS

Science **318**, 1917 (2007)

Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells

Junying Yu,[1,2]* Maxim A. Vodyanik,[2] Kim Smuga-Otto,[1,2] Jessica Antosiewicz-Bourget,[1,2] Jennifer L. Frane,[1] Shulan Tian,[3] Jeff Nie,[3] Gudrun A. Jonsdottir,[3] Victor Ruotti,[3] Ron Stewart,[3] Igor I. Slukvin,[2,4] James A. Thomson[1,2,5]*

Cell *131*, 861–872, November 30, 2007 ©2007 Elsevier Inc.

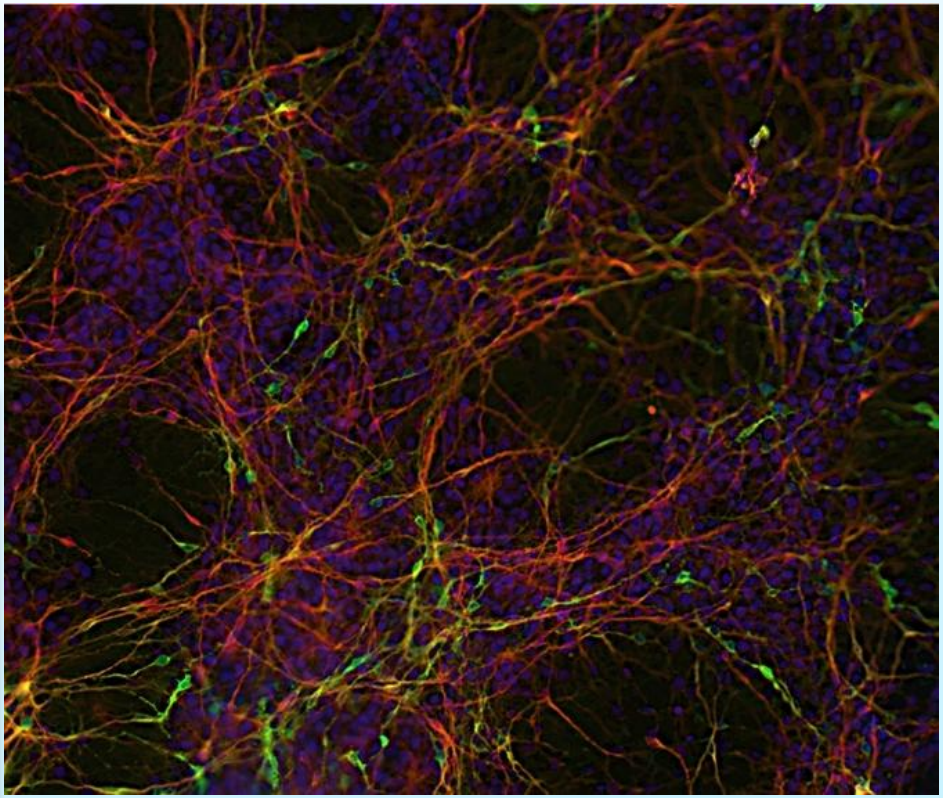
Cell

Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi,[1] Koji Tanabe,[1] Mari Ohnuki,[1] Megumi Narita,[1,2] Tomoko Ichisaka,[1,2] Kiichiro Tomoda,[3] and Shinya Yamanaka[1,2,3,4,*]

[1]Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2]CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
[3]Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, USA
[4]Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8507, Japan

Map2, **TH**, **DAPI**

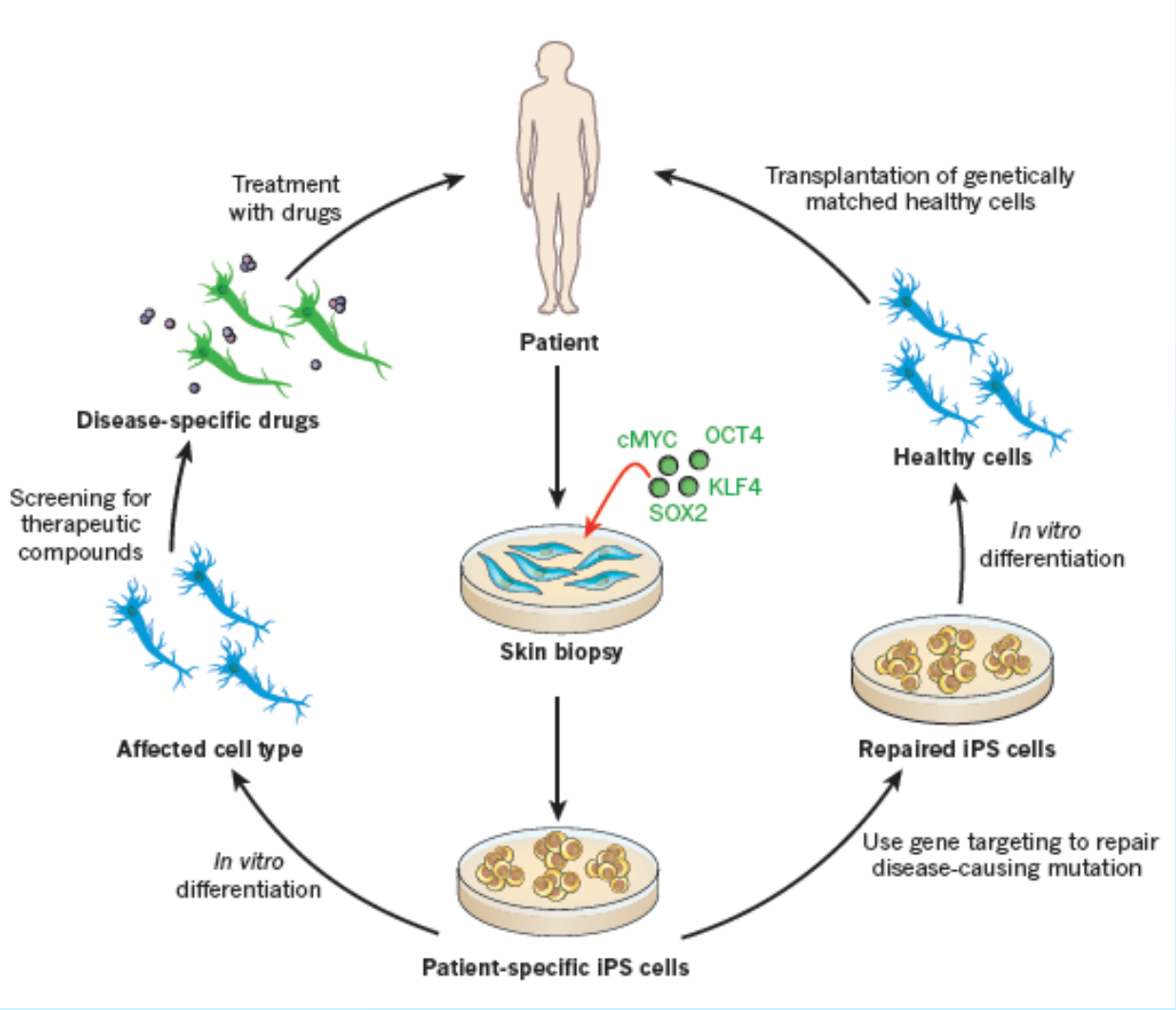


Dolmetsch lab, 2012

HEALTH & HUMAN SERVICES, USA — NATIONAL INSTITUTES OF HEALTH

Transformative Technologies – iPS cells

Disease in a dish for Rx screening



Personalized cell Rx

Nature, Jan 19, 2012 vol 481

Cell Biology: dendrite dynamics in Timothy syndrome derived neurons

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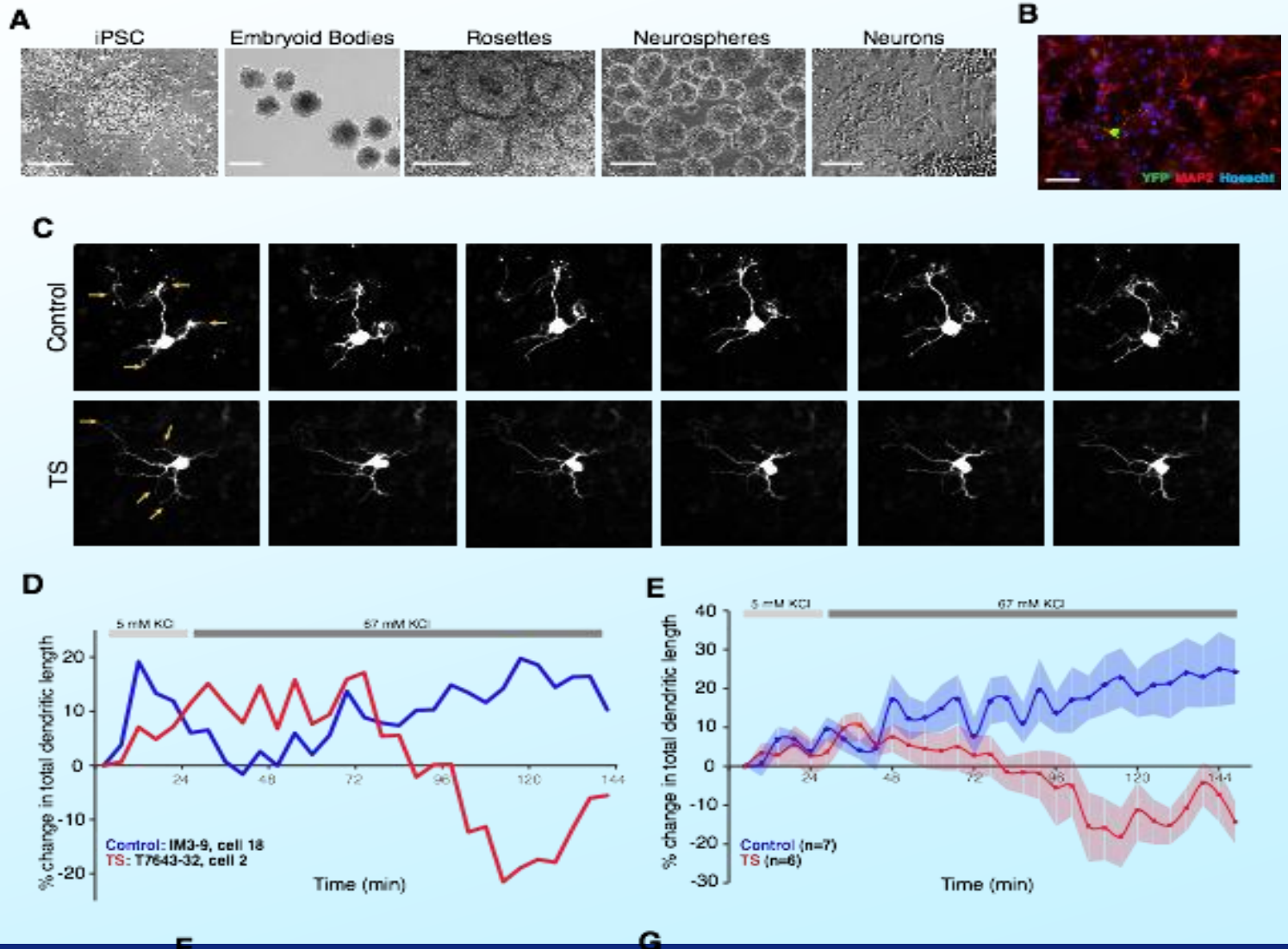
Source: Pasca and Dolmetsch



Cell Biology: What Have We Missed

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Are mental disorders cell autonomous?

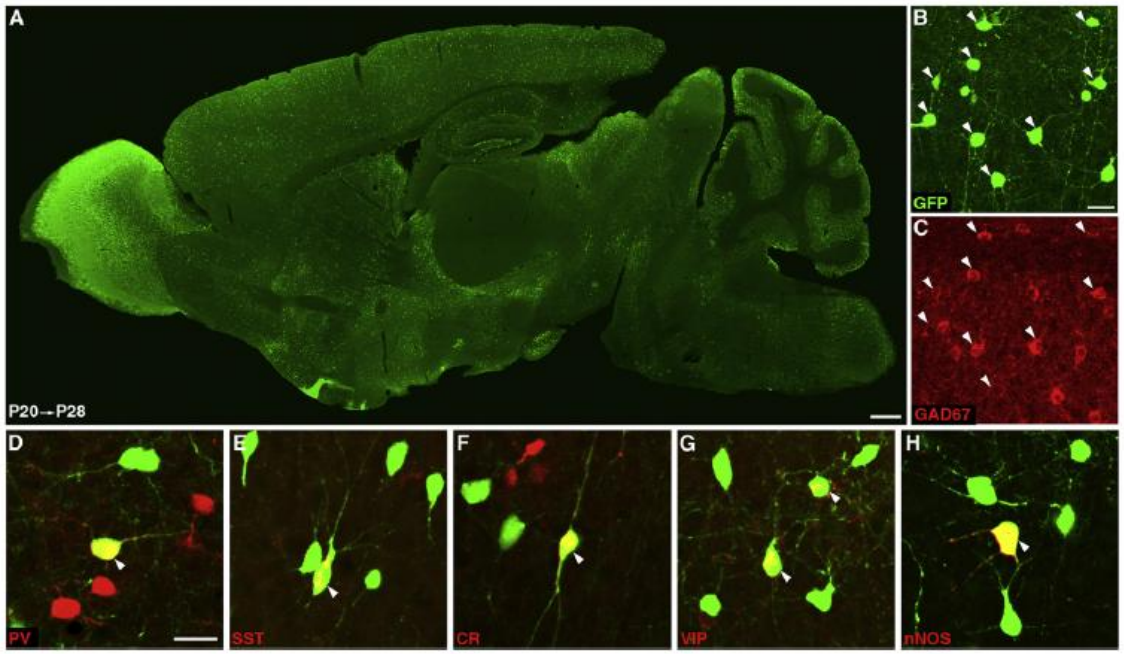
Neuron

NeuroResource

Cell PRESS

A Resource of Cre Driver Lines for Genetic Targeting of GABAergic Neurons in Cerebral Cortex

Hiroki Taniguchi,[1] Miao He,[1] Priscilla Wu,[1] Sangyong Kim,[1] Raehum Paik,[1] Ken Sugino,[2] Duda Kvitsani,[1] Yu Fu,[1] Jiangteng Lu,[1] Ying Lin,[1] Goichi Miyoshi,[3] Yasuyuki Shima,[2] Gord Fishell,[3] Sacha B. Nelson,[2] and Z. Josh Huang[1,*]



Systems: Transforming Technology

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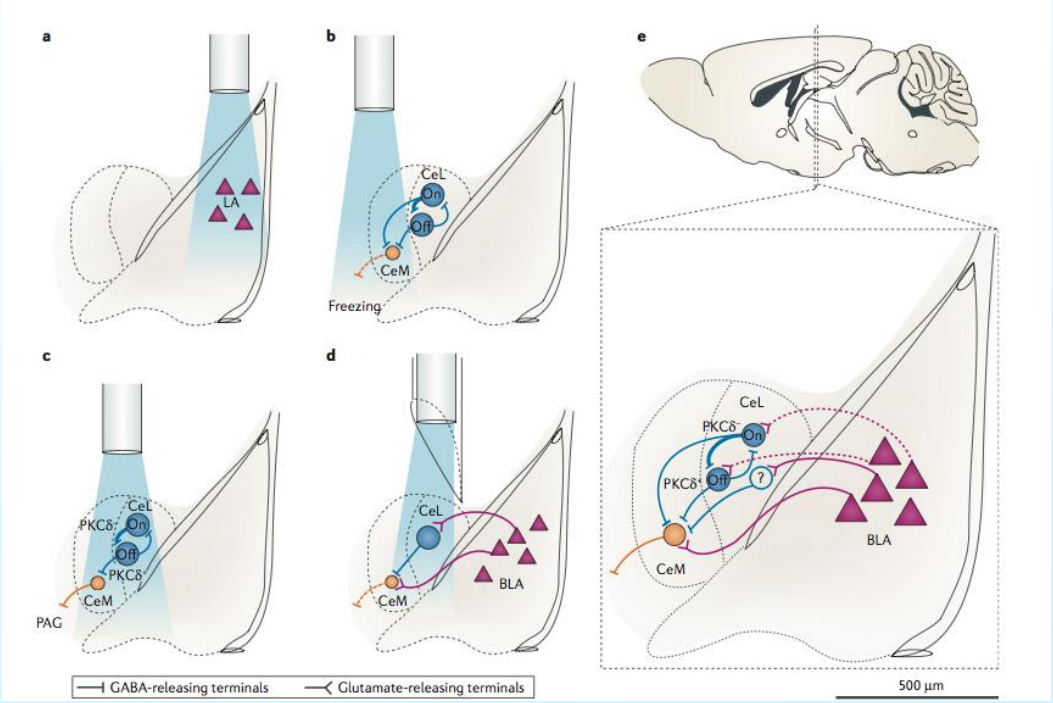
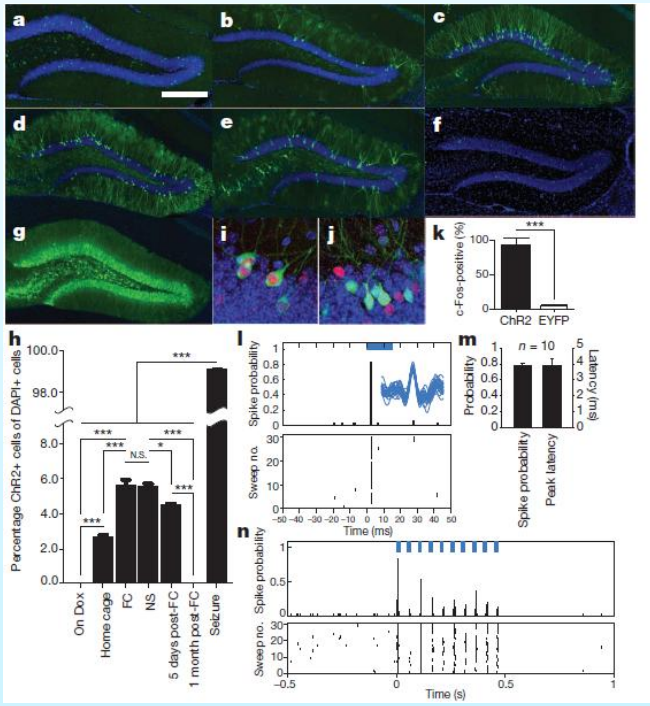
Optogenetics for Manipulating Circuits

Functional dissection of amygdala microcircuitry using optogenetic tools



Tye and Disseroth, Nat Neurosci Rev 2012

Optogenetic reactivation of hippocampal neurons after fear conditioning. Light-induced fear memory recall.



Liu et al., Nature 2012

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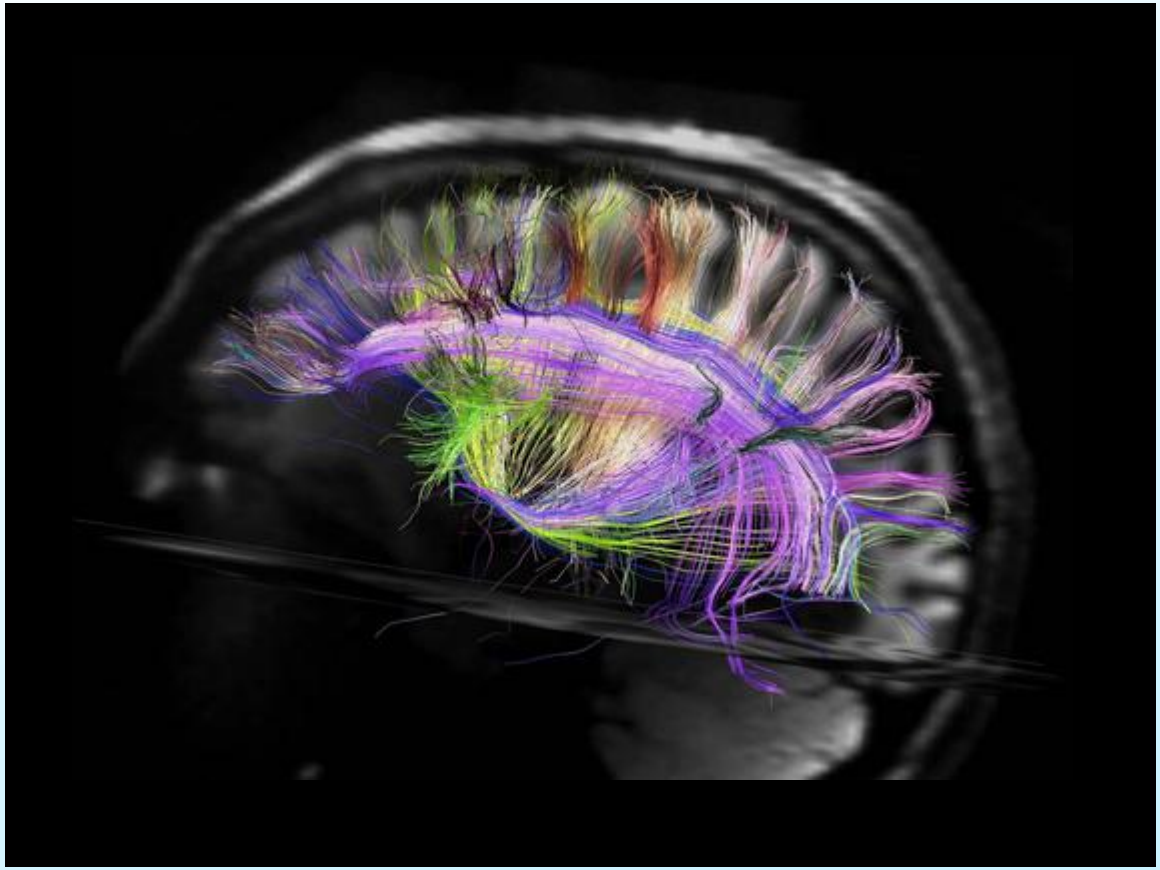
Mapping the Connectome: From DTI to DSI



Wedeen V.J, Science, 2012

Systems: What Have We Missed?

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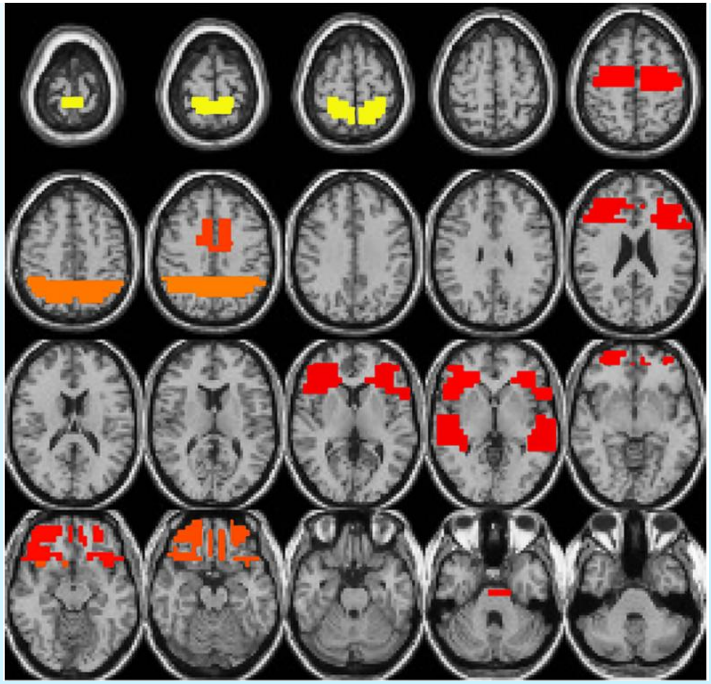
Biomarkers: Individual data

frontiers in HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 25 October 2010
doi: 10.3389/fnhum.2010.00192

A hybrid machine learning method for fusing fMRI and genetic data: combining both improves classification of schizophrenia

Honghui Yang[1,2], Jingyu Liu[2,3], Jing Sui[2,3], Godfrey Pearlson[4,5] and Vince D. Calhoun[2,3,5,6]*



Systems: What Have We Missed?

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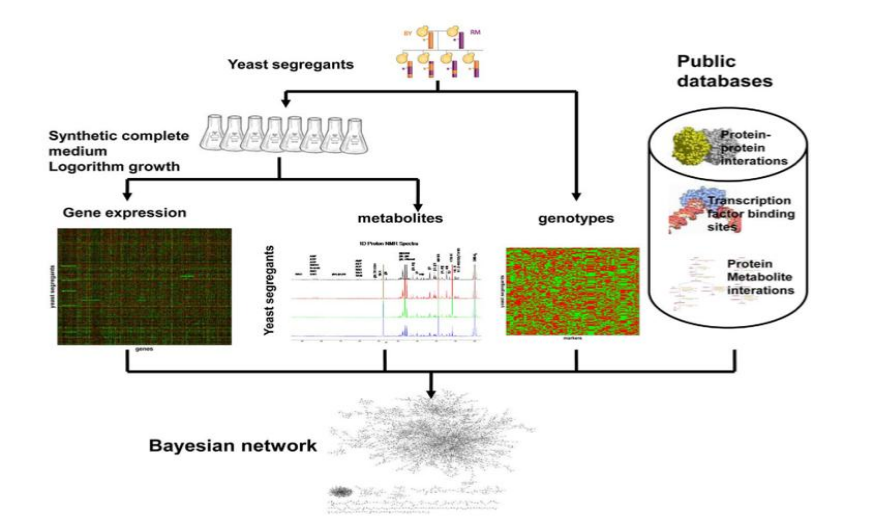
"Embracing Complexity"

OPEN ACCESS Freely available online

PLoS BIOLOGY

Stitching together Multiple Data Dimensions Reveals Interacting Metabolomic and Transcriptomic Networks That Modulate Cell Regulation

Jun Zhu[1*☯], Pavel Sova[2☯], Qiuwei Xu[3☯], Kenneth M. Dombek[2], Ethan Y. Xu[3], Heather Vu[3], Zhidong Tu[4], Rachel B. Brem[5], Roger E. Bumgarner[2], Eric E. Schadt[6*]



Individual: Transforming Technologies

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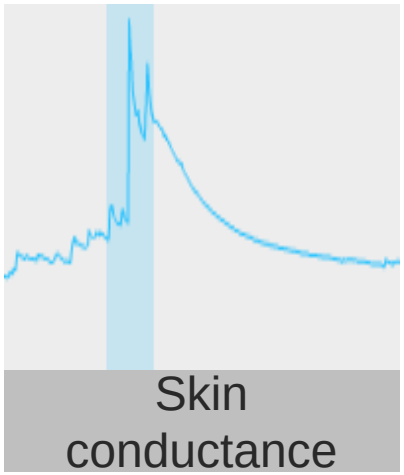
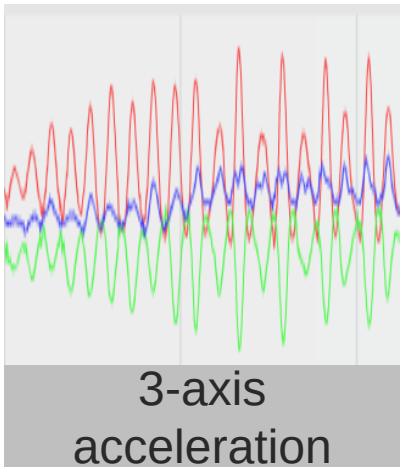
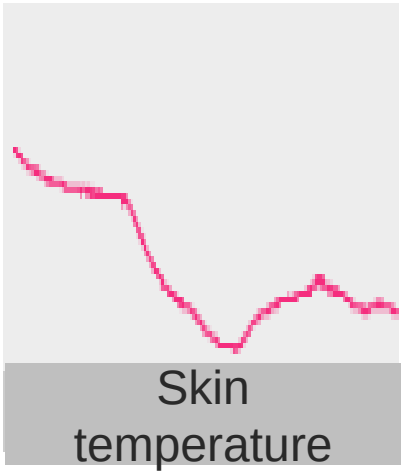
Objective Measures



Skin conductance



3-axis acceleration



Skin temperature

Activity, Sleep, EDA, EKG, EEG, Stereotypies, Temp.

Non-invasive 24/7 inexpensive phenotyping

MIT MEDIA LAB

Roz Picard and colleagues

Individual: What are we missing? Research Domain Criteria

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Schizophrenia

Cognitive Dysfunction

Depression

Cognitive Systems Domain

- Attention
- Perception
- Cognitive Control

Working Memory

- Language Behavior
- Declarative Memory

Units of Analysis

- Behavior
- Physiology
- Circuits
- Cells
- Molecules
- Genes

Insel et al, AJP, 2010

Individual : What are we missing?

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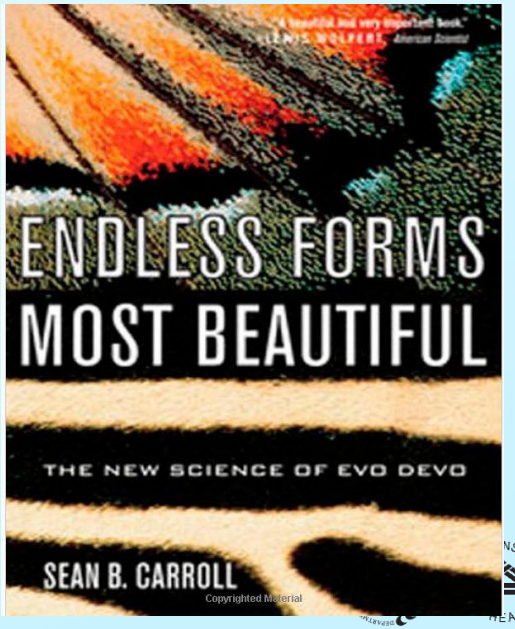
Behavioral and Biological Diversity

Species developed by genetic engineering over 70 million years:

- Number of vertebrates: > 50,000
- Number of mammals: 5,700
- Number of primates: 225

Species representing >98% of neuroscience research:

- Number of vertebrates: 5
- Number of mammals: 4
- Number of primates: 2



Social: Transforming Technologies
Crowd Sourcing

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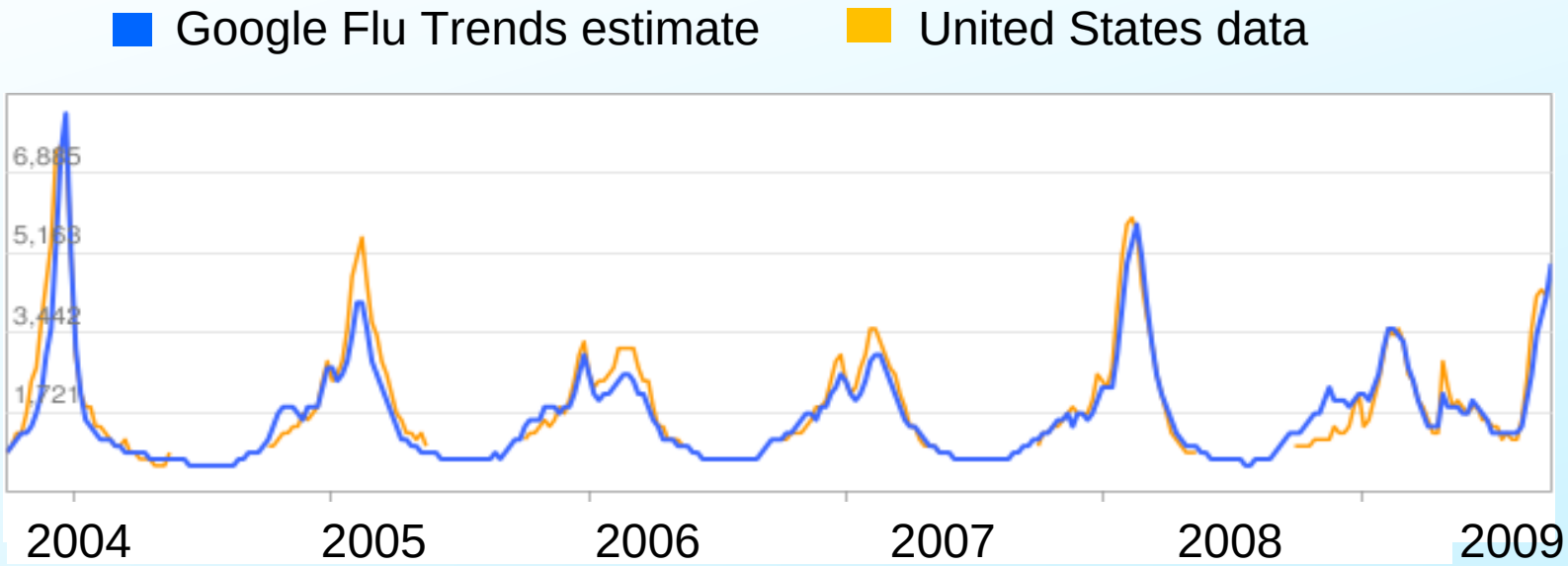
United States Flu Estimate



United States: Influenza-like illness (ILI) data provided by the U.S. Centers for Disease Control

From the Google Flu Trends web site: www.google.org/flutrends/

Social: Transforming Technologies
Crowd Sourcing

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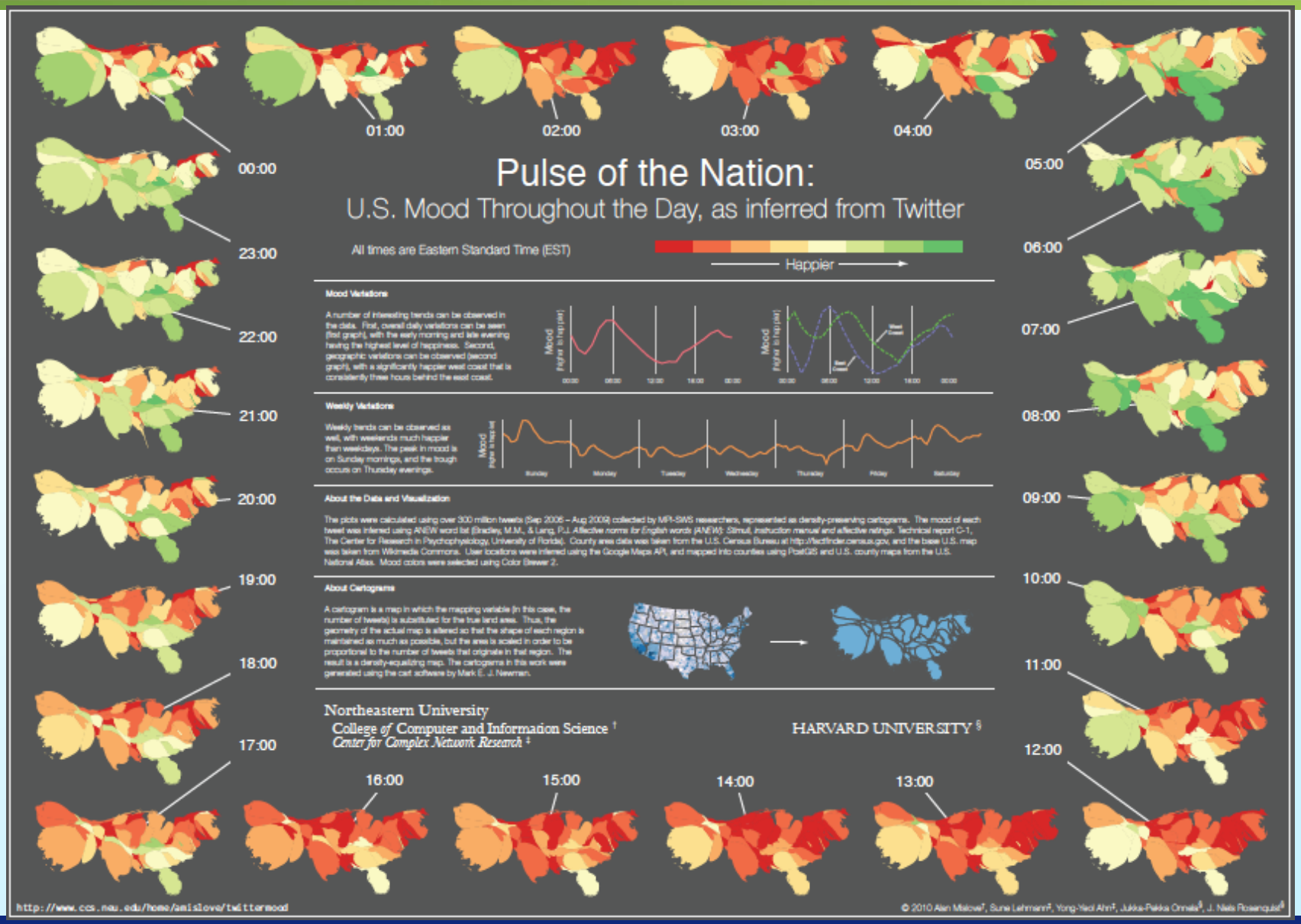

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Social: Transforming Technologies

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Crowd sourcing science:
RNA nanostructure as a Rubik's Cube

Multi-level Scientific Approach: Our Toolbox for Pathophysiology

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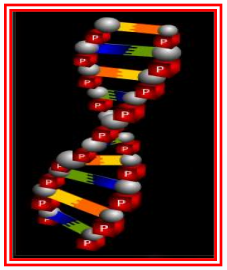



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Knock-outs	Optical	Imaging	Tools	Crowd Sourcing
Epigenetics	imaging	ChR-2	Epidemiology	
Databases	Databases	Databases	Databases	Databases

Not Only What, But How?

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- Data Standardization
- Data Integration
- Data Sharing
- Crowdsourcing

NDAR National Database for Autism Research
Serving the autism research community

NITRC *The source for neuroimaging tools and resources*

Psychiatric Genomics Consortium

Trends in Drug Development: Eroom's Law

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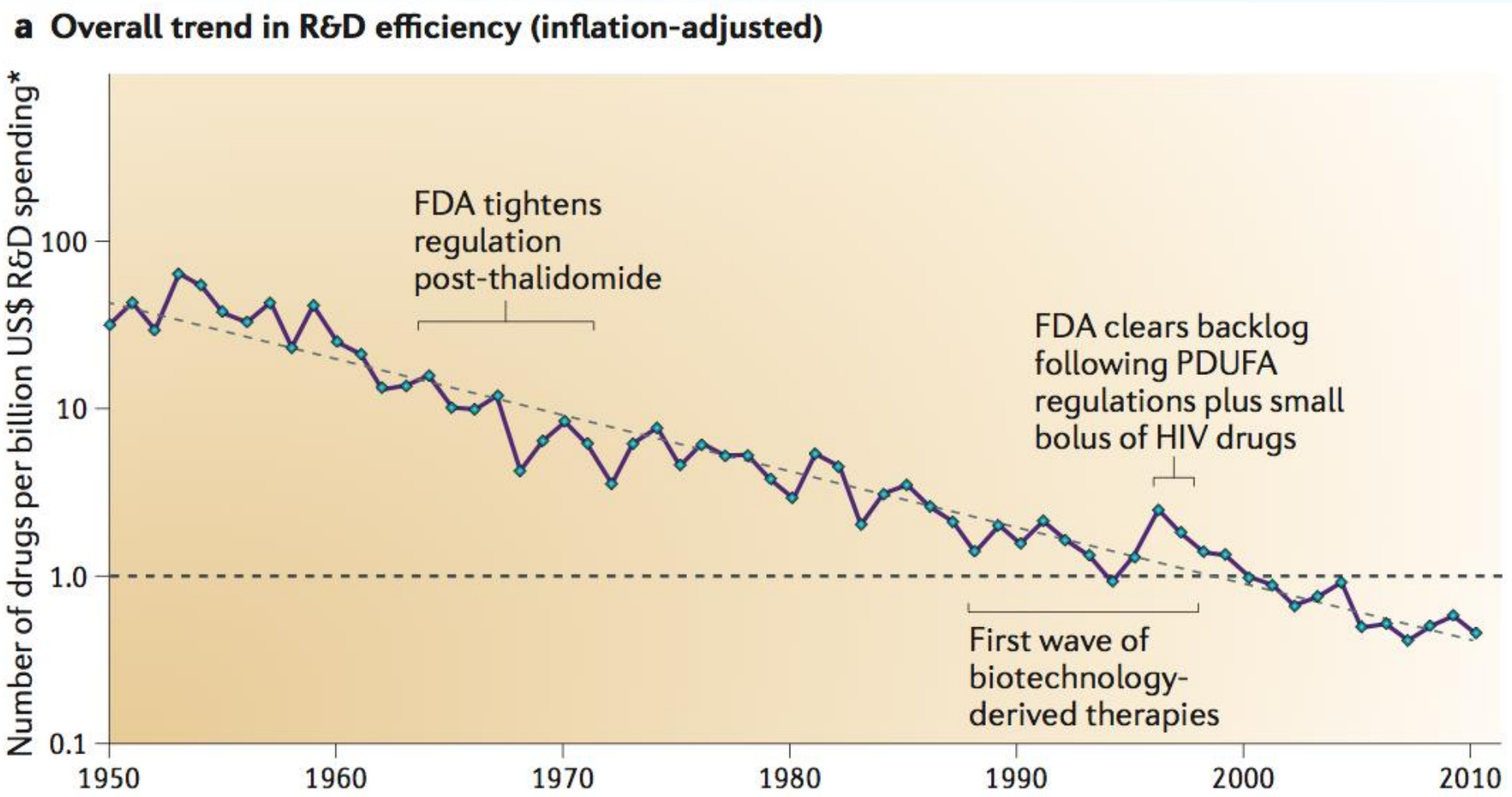

Scannell et al, NRDD, 2012

Advancing Translational Science: Experimental Medicine

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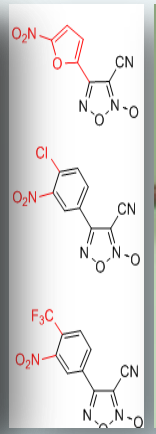
Trials to confirm or exclude targets; drugs as tools for fast fail

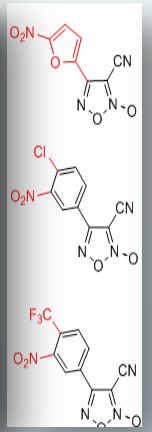


Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

New Paradigm: Experimental Medicine

- Move quickly into humans
- Focus on Phase 0 – Phase 2a
- Fail quickly and often
- Target engagement
- Precompetitive partnerships
- Share data

Advancing Translational Science: Repurposing

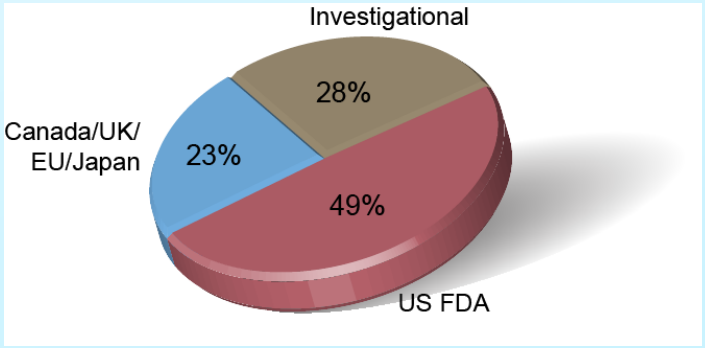


Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

NCATS Pharmaceutical Collection – Tools for Repurposing

Drug Source	In house	Procurement in process
US FDA	1635	182
UK/EU/Canada/Japan	756	177
Investigational	928	3953
Total Approved	2391	359
Total	**3319**	**4312**

- **Informatics sources for NPC**
  - US FDA: Orange Book, OTC, NDC, Green Book, Drugs at FDA
  - Britain NHS
  - EMEA
  - Health Canada
  - Japan NHI
- **Physical sources for NPC**
  - Procurement from >70 suppliers worldwide
  - In-house purification of APIs from marketed forms
  - Synthesis



Drug plate composition

Transforming Training

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Psychiatry

Neurology

Genetics

Clinical Neuroscience

Dev. Biol.

Neuroscience

Cog. science

From Biological Psychiatry to Clinical Neuroscience

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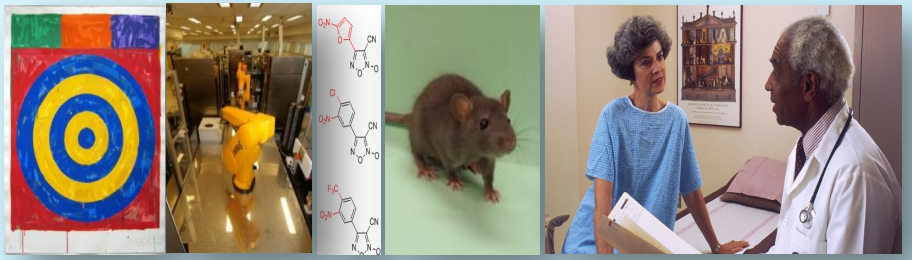
What we do? Frontiers of mental health research

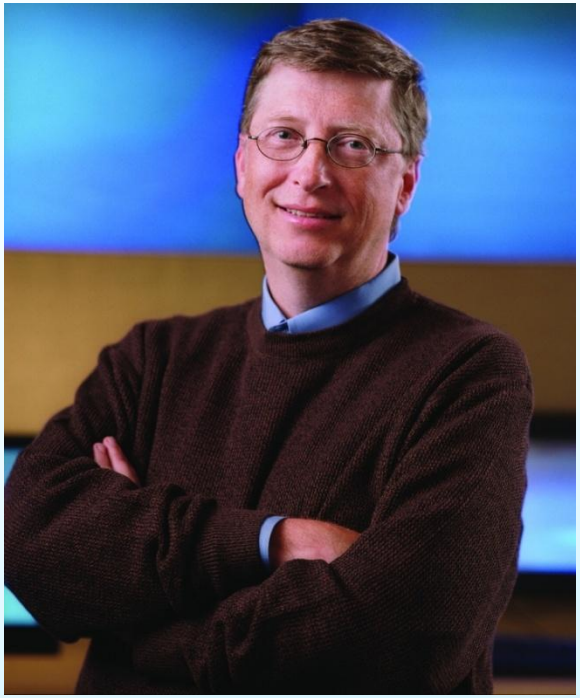
- Somatic mutations
- iPS cell transformation
- Individual imaging
- Sensor technology
- Crowd sourcing

How we do it? Changing the culture of mental health research

- Data sharing
- Experimental medicine
- Repurposing
- Transforming training



Finally



"We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten."

--Bill Gates Jr.